NTP NOMINATION HISTORY AND REVIEW

CUMENE

CAS No. 98-82-8

NOMINATION HISTORY

1.	Nomination Source:	NIEHS
2.	Recommendations:	- Carcinogenicity
3.	Rationale/Comments:	- High production - Potential human exposure (worker, environmental, and consumer) - Evidence of mutagenic activity - Lack of carcinogenicity testing
4.	Priority:	
5.	Date of Nomination:	

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(3/96)

SUMMARY OF DATA FOR CHEMICAL SELECTION

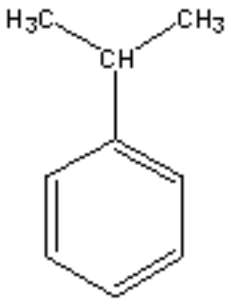
CHEMICAL IDENTIFICATION

CAS Registry Number: 98-82-8

Chemical Abstracts Service Name: Benzene, (1-methylethyl)- (9CI)

Synonyms: Cumene; cumol; isopropylbenzene; isopropylbenzol; 2-phenylpropane; AI3-04630

Structure, Molecular Formula and Molecular Weight:



C_9H_{12} Mol. wt.: 120.19

Chemical and Physical Properties

Description: Colorless liquid with a sharp, penetrating aromatic or gas-like odor (Budavari, 1989; NIOSH, 1990; Cavender, 1994)

Boiling Point: 152.4˚C (Lide, 1995)

Melting Point: -96.0˚C (Lide, 1995)

Density: 0.8618 g/cm^3 at 20˚C (Lide, 1995)

Refractive Index: 1.4915 at 20˚C (Schulz *et al*., 1993); 1.489 at 25˚C (Lewis, 1993)

Solubility: Insoluble in water; miscible in acetone, benzene, and ethanol (Lide, 1995)

Vapor Pressure: 3.2 mm Hg at 20˚C; relative vapor density (air = 1), 4.13 (Verschueren, 1983)

Octanol/water partition coefficient: log P = 3.66 (Verschueren, 1983)

Flash Point: 39˚C, closed cup (Budavari, 1989)

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Reactivity: Combustible (Lewis, 1993); incompatible with oxidizers, nitric acid, and sulfuric acid; forms cumene hydroperoxide upon long exposure to air (NIOSH, 1994)

Technical Products and Impurities: Cumene is available in technical, research, and pure grades (Lewis, 1993). Aldrich Chemical Co. (1994) offers cumene at 98% and 99% purity, neat standard for EPA methods, and a single component standard for EPA methods.

Cumene sold as merchant grade for chemical purposes is usually produced with a 99.9 wt % minimum with the following maximum specifications: ethylbenzene, 200 ppm; *n*-propylbenzene, 300 ppm; butylbenzenes, 200 ppm; bromine index, 50; and sulfur compounds (as ppmw S), 1. Captively manufactured cumene typically is not held to such strict values, although 99.9% purity is common (Schulz *et al*., 1993).

Ashland Chemical, Inc. and Chevron Chemical Co. offer cumene in tank car, tank truck, and barge quantities (Kuney, 1994).

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EXPOSURE INFORMATION

Production and Producers: Cumene as a pure chemical intermediate is produced in modified Friedel-Crafts reaction processes that use acidic catalysts to alkylate benzene with propylene. The majority of cumene is manufactured with a solid phosphoric acid catalyst. The remainder is made with aluminum chloride catalyst (Schulz *et al*., 1993).

The most common process for making cumene uses an adiabatic reactor for the exothermic alkylation. A significant portion of the heat of reaction is recovered in preheating the feed and rectifying the effluent to generate a portion of the benzene recycle. Cumene product purification includes recovery of the remaining benzene, clay treatment, and fractionation to remove small amounts of olefin oligomers and heavy material, respectively. The propylene feed may either be pure or contain a substantial amount of propane, which can come from a refinery fluid catalytic cracking operation. However, the feed must be essentially free of ethylene and butylenes to avoid contamination of the product with ethyl- and butylbenzenes (Schulz *et al*., 1993). Several other catalyst systems have been suggested, including boron fluoride and both crystalline and noncrystalline silicas and aluminosilicates. Although no commercial facility exists, the concept of using a crystalline silica or aluminosilicate catalyst in an integral reaction and distillation apparatus has been proposed (Schulz *et al*., 1993).

The annual production of cumene in the United States is large—it was ranked 32nd in 1993, 31st in 1994, and 30th in 1995 of the top 50 organic and inorganic chemicals. Production statistics for 1984 to 1995, presented in Table 1, show a growth rate of 5.3% for 1985-1995, 18% for 1993-1994, and 7.8% for 1994-1995 (Anon., 1995, 1996). Nearly half of cumene is made captively (i.e., produced at the site and then further processed to phenol at the same site) (Schulz *et al*., 1993).

Year	Production (millions of lbs)
1984	3,754
1985	2,627
1986	3,745
1987	4,105
1988	4,455
1989	4,426
1990	4,311
1991	4,168
1992	4,666
1993	4,393

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1994	5,163
1995	5,630

The major US producers of cumene are Amoco, Ashland Chemical, Inc., BTL, Chevron Chemical Co., Citgo, Coastal, Georgia Gulf, Koch Refining, Shell, and Texaco Chemical Co. (Anon., 1993).

Imports of cumene were 380 million lbs in 1991 and 450 million lbs in 1992. Exports of cumene in 1992 were nearly 75 million lbs (Anon., 1993).

Use Pattern: Cumene is the principal chemical used in the production of phenol and its coproduct, acetone, via the chemical intermediate cumene hydroperoxide. It is also used as a starting material in the production of acetophenone, a-methylstyrene, diisopropylbenzene, and dicumylperoxide. Minor uses of cumene include as a thinner for paints, enamels, and lacquers; as a constituent of some petroleum-based solvents, such as naptha; in gasoline blending diesel fuel, and high-octane aviation fuel; and as a raw material for peroxides and oxidation catalysts such as polymerization catalysts for acrylic and polyester-type resins. It is also a good solvent for fats and resins and, as such, has been suggested as a replacement for benzene in many of its industrial applications (Parmeggiani, 1983; Verschueren, 1983; Mannsville Chemical Products Corp., 1985; Budavari, 1989; ACGIH, 1993; Anon., 1993; Lewis, 1993; Schulz *et al*., 1993; NLM, 1996a).

Cumene consumption is related directly to phenol demand which depends principally on the construction, automotive, and electrical industries. Demand was 4.2 billion lbs in 1987, 4.6 billion lbs in 1992 (includes exports), and is projected to be 5.1 billion lbs in 1997. In 1992, consumption was 95% for phenol and acetone production and 5% for a-methylstyrene and other miscellaneous uses. Cumene is used captively by BTL, Georgia Gulf, Shell, and Texaco to produce phenol and acetone. Amoco consumes its production internally to make a-methylstyrene (Mannsville Chemical Products Corp., 1985; Anon., 1993; Schulz *et al*., 1993).

Human Exposure: There is potential for occupational and environmental exposure to cumene.

Occupational

Cumene is a major commodity chemical, and there is potential for many workers to be

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exposed. The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 14,268 workers, including 2,760 female employees, were potentially exposed to cumene in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NIOSH, 1990).

Work area and monitoring samples from cumene producers and processors have been reported as follows: distillation, 0.0001-3.35 ppm with a 0.45 ppm mean; oxidation, 0.0001-5.58 ppm with a 0.93 mean; laboratory, 0.34-0.44 ppm with a 0.39 ppm mean; repair, 0.16-2.50 ppm with a 1.33 ppm mean; recovery, 0.001-1.20 ppm with a 0.31 ppm mean; cumene unit, 0.078-0.620 ppm with a 0.189 ppm mean. Gasoline delivery truck drivers are exposed to air containing from 0.01-0.04 ppm cumene. Cumene levels were 60-250 $\mu g/m^3$ in shoe factory air and 2-200 $\mu g/m^3$ in the vulcanization area and not detected-10 $\mu g/m^3$ in the extrusion area of tire retreading plant. No information was available to indicate whether or not these values were typical of the tire retreading industry (NLM, 1996a).

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Environmental

Cumene is a contaminant of air, sediments, and surface, drinking, and ground water and is a natural constituent of a variety of foods and vegetation. General population exposure to cumene is expected to result primarily from inspiration of air contaminated with cumene from evaporation of petroleum products, but additional exposure may result from ingestion of food. Little exposure is expected to result from ingestion of water (NLM, 1996a).

Two studies have detected cumene in human expired air from non-smoking individuals. One study found a level of 0.13 µg/hr while the other study did not quantify the level (NLM, 1996a).

Environmental Occurrence: Cumene is released to the environment as a result of its production and processing, during its transport, from petroleum refining and the evaporation and combustion of petroleum products, during the transportation and distribution of motor fuels, and by the use of a variety of products containing cumene. Cigarette tobacco also releases cumene during consumption. Cumene release from all these sources was estimated to be 21 million lbs annually. Other, unquantifiable anthropogenic cumene releases include operations involving vulcanization of rubber, building materials, jet engine exhaust, outboard motor operations, solvent uses, paint manufacture, pharmaceutical production, and textile plants. Cumene is also released to the environment in effluents from leather tanning, iron and steel manufacturing, paving and roofing, paint and ink formulation, printing and publishing, ore mining, coal mining, organics and plastics manufacturing, pesticide manufacturing, electroplating, and pulp and paper production (NLM, 1996a).

Natural occurrence

Cumene occurs naturally in petroleum crudes and coal tar (Verschueren, 1983). It also occurs in a variety of natural substances including essential oils from plants, marsh grasses, and a variety of foodstuffs. Trace quantities have been detected in papaya, Sapodilla fruit, and Australian honey. Cumene has been detected but not quantified in fried chicken, tomatoes, Concord grapes, cooked rice, oat groats, baked potatoes, Beaufort cheese, fried bacon, dried legumes (beans, split peas, lentils), southern pea seeds, and Zinfandel wine (NLM, 1996a).

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Air

Air samples have also been found to contain cumene. Samples collected from the Milwaukee plume over Lake Michigan in 1976 contained 0.1 ppb. Two air samples collected over Lake Michigan (1000 to 3000 foot altitude) also contained cumene (0.49 µg/m^3). Several studies have quantified cumene in Los Angeles air samples. These studies recorded average concentrations of 3 ppb with a maximum of 12 ppb in 1966, a range of not detected to 9.8 µg/m^3, a range of <2.45-36 µg/m^3 with a mean of 16.66 µg/m^3, and a mean of 14.7 µg/m^3 with a maximum of 144 µg/m^3. Cumene has also been detected in air samples from and near Houston; from the Smokey Mountains National Park, TN (near campfires); at a Shell Oil Refinery in TX; from Elizabeth, Newark, Batsoto, and South Amboy, NY; from Pullman, WA; and from the Allegheny Mountain Tunnel, PA (NLM, 1996a).

Water

Several studies have identified cumene as a water contaminant. In ground water, cumene has been found in samples from all 50 states and Puerto Rico; at 30, 15, 2.5, 1.3, and 0.01 ppb in samples taken in progressive distances downgradient from an aviation fuel spill; at an average concentration of 35 µg/l in samples taken near an underground coal gasification site; and at concentrations of 27, 59, and 19 ppb in samples taken near two underground gasification sites in northeastern Wyoming. Analysis of water samples of offshore oil production platforms for cumene found 140 ppb in a petroleum formation water sample, but none in the water or gas samples of underwater vent plumes. Cumene has also been detected, but not quantified, in surface water samples from Narraganset Bay, Rhode Island. Drinking water samples from US cities have also been found to contain cumene. In addition, cumene has been detected in sediment (NLM, 1996a).

Regulatory Status: The ACGIH-recommended threshold limit value-time weighted average (TLV-TWA) for cumene is 50 ppm (246 mg/m^3), with a skin notation. A short-term exposure limit (STEL) has not been determined (ACGIH, 1995). The OSHA permissible exposure limit (PEL) is 50 ppm (245 mg/m^3), with a skin designation, averaged over an eight-hour work shift. A STEL has not been determined (OSHA, 1994). The NIOSH-recommended exposure limit for cumene is 50 ppm (245 mg/m^3), with a skin notation, averaged over a 10-hour work shift (NIOSH, 1994).

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to cumene and cancer risk in humans were identified in the available literature.

Cumene is an eye, skin, and mucous membrane irritant (NIOSH, 1994). Short-term exposure to cumene may cause dizziness, headache, drowsiness, slight incoordination, and unconsciousness (NLM, 1996a).

Animal Data:

Acute

Studies on the acute toxicity of cumene show a 7-hour LC_{50} of 2,000 ppm for mice, an oral LD_{50} for male rats of 1.4 g/kg body weight, an oral LD_{50} for mice of 12.75 g/kg body weight, and a dermal LD_{50} for rabbits of 12.3 ml/kg. Mice exposed to the vapors of cumene showed dilation of cutaneous blood vessels, and grades of central nervous system depression, depression of respiration, and death, depending on the concentration and duration of exposure. The narcosis is characterized by slow induction and long duration, relative to benzene and toluene. Cumene is an eye and skin irritant in rabbits (ACGIH, 1993; NLM, 1996b).

Subchronic

Several subchronic studies have been conducted on cumene.

- Oral. When rats were dosed by repeated gastric intubation of 154 mg cumene/kg body weight for 194 days, no evidence of injury was found. At a higher dosage (462 mg/kg), an increase in the weight of kidneys was observed (ACGIH, 1993).

- Topical. Subcutaneous application of 1 ml cumene/kg daily for 2 weeks did not lower the femoral marrow cell population of rats (ACGIH, 1993).

- Inhalation. Exposure of rats at 500 ppm cumene daily for 5 months resulted in no significant changes in the peripheral blood; however, hyperemia and congestion were noted in the lungs, liver, and kidneys of exposed animals (ACGIH, 1993). Exposure of rabbits to 1323 ppm (6496 mg/m^3) for up to 180 days resulted in no changes in behavior or body weight gain while exposure of rats to 509 ppm (2499 mg/m^3) for 180 days produced a decrease in body weight gain limited to the initial part of the study and congestion of the lung, liver, spleen, kidneys, and adrenals. Higher exposure levels—814 ppm (3997 mg/m^3) and 1323 ppm (6,496 mg/m^3)—killed the rats within 16 hours of exposure (Fabre *et al*., 1955). A later subchronic inhalation study, however, found essentially negative findings in rats, guinea pigs, dogs, and monkeys exposed for 8 hours/day, 5 days/week for either 30 exposures to 244 ppm (1195 mg/m^3) or continuously to 3.7 ppm (18 mg/m^3) or 30 ppm (146 mg/m^3) for 90 days (Jenkins *et al*., 1970).

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Subchronic exposure of rats to cumene vapor resulted in mild toxicity at 1200 ppm, minimal effects at 500 ppm, no observable effects at 50 and 100 ppm, and no neurotoxicity or ototoxicity. Groups of 21 male and 21 female Fischer 344 rats were exposed to cumene vapor at 0, 100, 500, and 1200 ppm (mean analytical concentration of 100, 496, and 1202 ppm, respectively) for 6 hours/day, 5 days/week, for 13 weeks. A subsequent 13-week study with a 4-week recovery period was conducted in groups of 15 male and 15 female rats at 0, 50, 100, 500, and 1200 ppm. There were no exposure-related changes in the functional observational battery, auditory brain stem response, brain measurements, or nervous system histopathology. Motor activity decreases seen only in male rats exposed to 500 or 1200 ppm in the first study were not replicated in the second study. The 500- and/or 1200-ppm groups showed transient decreases in body weight gain and food consumption, increase in water consumption, and changes in several hematologic and clinical chemistry parameters. There were no exposure-related ophthalmologic findings or effects on spermatogenesis. Weights of liver, kidneys, and adrenal glands were increased in the 500- and 1200-ppm groups. Renal proximal tubular cell hypertrophy, hyperplasia, and hyaline drop formation were observed in the male rats at 500 and 1200 ppm; however, the male rats do not appear to be a good model for assessing human risk of this type of nephropathy (Dodd & Kintigh, 1989; Cushman *et al*., 1995).

Chronic

No 2-year carcinogenicity studies of cumene in animals were identified in the available literature.

Short-Term Tests: Several studies have demonstrated that cumene is not mutagenic in bacteria. While one study found a positive mutagenic response in spot tests with *Salmonella typhimurium* strain TA100, a later study by the same researchers did not find evidence of mutagenicity in extensive tests in agar as well as in desiccators with strains TA98, TA100, TA1535, TA1537, and TA1538 (5 mg/plate or a dose which gave a toxic response, whichever was greater) or in *Saccharomyces cerevisiae* (0.2 ml or 10^{-3} and 10^{-5} dilutions) (Tardiff *et al*., 1976; Simmon *et al*., 1977). More recent studies also found that cumene was not mutagenic with or without S9 toward strains TA98, TA100, TA1535, or TA1537 at concentrations up to 0.2 mg/plate in plate incorporation tests or at concentrations up to 20 µl/spot in spot tests (Flowers, 1982; Lawlor & Wagner, 1987). In a screening of tobacco smoke constituents for mutagenicity in the Ames assay, cumene tested negative in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 at concentrations up to 30 µmol/plate both with and without metabolic activation (liver fraction from Aroclor 1254-induced rats in all strains and from methylcholanthrene-induced rats in strains TA98 and TA100); at 3 µmol/plate, toxicity was noted (Florin *et al*., 1980). Addition of cumene (about 10% by volume) to diesel fuel did not increase the direct-acting mutagenicity of particle extracts or mutagenicity emission rates in *S. typhimurium* (test strains not specified)

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without addition of S9 (Jensen *et al*., 1988).

Cumene did not induce point mutations in the CHO/HGPRT test when tested at concentrations up to 26 µg/ml, both with and without S9 (Gulf Life Sciences Center, 1985a). A critique of this study noted that variability in spontaneous mutant frequencies and colony forming efficiencies were sufficient to warrant further testing (Maslansky, 1986). A later study, however, also found that cumene was negative at doses up to 125 µg/ml (cloning efficiency was ≤ 10% at higher doses) without S9 and at doses levels up to 225 µg/ml with S9 in the CHO/HGPRT assay (Yang, 1987).

Cumene did not induce chromosome damage in *in vitro* tests with CHO cells or in *in vivo* tests with mouse bone marrow cells. CHO cells were treated with cumene at doses up to 200 µg/ml without S9 and up to 225 µg/ml with S9. High toxicity was observed at the high concentration levels, both with and without S9. A small increase in the frequency of chromosomal aberrations was observed with S9 at 156 µg/ml, but the frequency was within the historical control range. No increase in the frequency of chromosomal aberrations was observed at other treatment levels, either with or without S9 (Putman, 1987a). In Crl:CDR-1(ICR)BR Swiss mice (10-15 mice/sex/dose group) treated by gavage with cumene dose levels of 0.0, 0.25, 0.50, or 1.0 g/kg bw/day for 2 days (the high-dose group was treated only once) and then sacrificed 0-2 days later, the frequency of micronucleated polychromatic erythrocytes in bone marrow was not increased (Gulf Life Sciences Center, 1985b).

C_9 aromatic hydrocarbons containing 2.74% cumene did not induce chromosome or chromatid aberrations in the bone marrow of Sprague-Dawley rats (groups of 15 males and 15 females) exposed 6 hours/day for 5 consecutive days to vapor concentrations up to 1500 ppm (actual concentrations up to 1540 ppm) (International Research and Development Corp., 1987).

Cumene induced morphological transformation *in vitro* in BALB/3T3 mouse embryo cells when tested at 60 µg/ml; lower concentrations (5 and 20 µg/ml) did not elicit a positive response (Gulf Life Sciences Center, 1984a). An analysis of this study, however, considered the findings equivocal based on a positive response at only one dose and lack of a dose response; retesting was recommended (Maslansky, 1986). A later test found that cumene did not induce cell transformation in BALB/3T3 mouse embryo cells when tested

at concentrations up to 200 µg/ml without S9; concentrations ranging from 250 to 500 µg/ml were toxic (Putman, 1987b).

Cumene induced unscheduled DNA synthesis at 16 µg/ml and 32 µg/ml in a hepatocyte primary culture/DNA repair test with hepatocytes from Fisher 344 rats (Gulf Life Sciences Center, 1984b). An analysis of this assay noted that the DNA repair assay initially appears marginally positive but that there is no consistent response in replicate cultures exposed to cumene and that the high incidence of repair-positive cells in negative controls warrants invalidation of the assay (Maslansky, 1986). A later study, however, found that cumene did not induce unscheduled DNA synthesis in male Fischer rat primary hepatocytes when tested at doses up to 24 µg/ml; concentrations ranging from 32 to 120 µg/ml were cytotoxic (Curren, 1987).

Metabolism: The ACGIH (1993) summarized information reported in pharmacokinetic/metabolism studies as follows. Cumene is stated to be absorbed through the intact skin more rapidly than toluene, xylene, or ethyl benzene. A small quantity of the cumene absorbed in the blood is exhaled unchanged, but the major portion is metabolized in the liver and excreted in the urine as conjugated alcohols or acids.

Experiments on the absorption of cumene through the respiratory tract of 10 healthy volunteers exposed to cumene vapors of 240, 480, or 720 mg/m^3 under controlled conditions showed an average retention time of cumene vapors of about 50% and excretion within 48 hours of about 35% in urine as dimethylphenylcarbinol (Senczuk & Litewka, 1976).

Cumene is absorbed readily in mammals and is oxidized at the side chain, forming dimethylphenylcarbinol glucuronide. In male albino rats gavaged with 100 mg/kg cumene, the 48-hour urinary metabolites were 2-phenyl-1-propanol and 2-phenyl-2-propanol. Similarly in rabbits, less than 5% cumene was exhaled unchanged following ingestion, and urinary metabolites were the glucuronides of 2-phenyl-2-propanol (40%), 2-phenyl-1-propanol (25%), and a-phenylpropionic acid (25%) (Gosselin *et al*., 1984; National Research Council, 1981; Cavender, 1994).

A study of the stereochemistry of the metabolites in rabbits gavaged with cumene identified four urinary metabolites. The major metabolite, 2-phenyl-2-propanol (85.7% of

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the total neutral fraction), was not optically active. Of the three optically active metabolites, 2-phenyl-1-propanol and 2-hydroxy-2-phenyl propanoic acid were *R* predominant, whereas with 2-phenylpropanoic acid, the *S*-isomer predominated. The investigators suggested that these results imply that preferential omega-hydroxylation occurs at the *pro-S* methyl group and that the oxidation is followed by stereochemical inversion of (*R*)-(-)-2-phenylpropanol to the corresponding (*S*)-(+)-acid (Ishida & Matsumoto, 1992).

The metabolism, disposition, and pharmacokinetic studies of cumene in rats following oral, iv, or nose-only inhalation administration demonstrated that cumene was well absorbed by any route. Following absorption, cumene was extensively metabolized and completely excreted. In general, very similar rates and routes of elimination were observed between dose routes, dose levels, and sex groups. Urine was the major route of elimination following any dose by any route. A minimum average of 70% of the dose was excreted in the urine. At lower doses or exposure levels of cumene, relatively little radiolabel was excreted in the expired breath or in the feces while almost all of the dose was eliminated to the urine. With increasing doses or exposure levels, greater amounts of radiolabeled material appeared in the expired breath and, to a much smaller extent, in the feces. Conjugated metabolites of cumene were excreted in the urine. In general over all doses and routes, 50% or more of urinary excretion was accounted for by 2-phenyl-2-propanol and its glucuronide and/or sulfate conjugates. The balance of excretion in urine was accounted for by conjugates of 2-phenyl-1,2-propanediol and an unknown metabolite, possibly phenylmalonic acid or a closely related metabolite. In addition, small amounts of the free, unconjugated cumene metabolites 2-phenyl-1,2-propanediol, 2-phenyl-2-propanol, and 2-phenylpropionic acid were detected (Slauter & Jeffcoat, 1989, 1990, 1992).

Other Biological Effects: The health, physical development, and clinical course adaptation of processes were studied, as well as immunologic and psychochemical indices in the blood of 347 newborns of laboratory workers and equipment operators in petroleum-chemical industries. Workplace air contaminants included aromatic hydrocarbons, cumene, and ethyl and butyl alcohols. Controls consisted of 1526 infants born to women who lived and worked in the administrative part of the city. The average indices of physical development of the newborns in the study group did not differ from children in the control group. However, the percentile distribution of the indicated parameters showed polarization of values of body weight in the youngsters studied; the specific weight of the children with

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body weight less than the 10th percentile and more than the 90th percentile was increased compared to these indices in the control group. Delay in intrauterine development occurred more often in the study group (24.2% ± 2.3%) than in controls (13.7% ± 0.9%; $P < 0.01$). Developmental defects were observed with identical frequency. Clinical processes of adaptation occurred with greater stress in the study group than in the control group and were characterized by an increase in frequency of illnesses with hypoxic or hypoxic-traumatic damage to the central nervous system, a hemorrhage syndrome, and allergic reactions in the form of toxic erythema and intertrigo. Significant changes were discovered in the hematologic and cytochemical indices of blood in the study group, with evidence of altered intensity of energy and enzyme metabolism of neutrophils (a decrease in the content of glycogen and lipids, an increase in peroxidase activity) and of chronic intrauterine hypoxia (average increase in the number of erythrocytes and leukocytes and delay in interception of curves of neutrophils and lymphocytes). The immunologic status is characterized by a decrease in the content of IgG and in the phagocyte index. The author suggests that these clinical and physiologic features are evidence that occupational danger in the petroleum-chemical industry is a risk factor not only for the reproductive function of the workers but also for their offspring (Akhmadeyeva, 1993).

An inhalation developmental toxicity study in mice with a C_9 aromatic hydrocarbon found evidence of maternal and developmental toxicity. Mated Charles River CD-1 female mice (groups of 30) were exposed to concentration levels of 100, 500, and 1500 ppm 6 hours/day of the test article on gestational days 6 through 15. The test article contained only 2.74% by weight cumene; other components included trimethylbenzenes (~55%), ethyltoluenes (~27.5%), *o*-xylene (3.2%), and *n*-propylbenzene (3.97%). Developmental toxicity was elicited at the 500 and 1500 ppm levels, as indicated by a significant ($P < 0.01$) increase in mean postimplantation loss at the 1500 ppm level and significant ($P < 0.01$) decrease in mean fetal body weights at the 500 ppm and 1500 ppm levels. Further evidence of an adverse effect on fetal development was the increased incidence of unossified sternebrae and reduced skull ossification at the 1500 ppm level when compared with the control group. Maternal toxicity was elicited at the 1500 ppm level. This was expressed as near 50% mortality, reduced food intake and inhibited body weight gain during the exposure and overall gestation periods, significant decreases in mean hematocrit ($P < 0.01$) and mean corpuscular volume ($P < 0.05$), and a significant increase ($P < 0.01$) in mean corpuscular hemoglobin concentration. An increase in the incidence of cleft palate was noted at the 1500 ppm level in relation to the control group, and due indirectly

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to the test article as a result of maternal stress (International Research and Development Corp., 1988).

Developmental toxicity studies of cumene in rats and rabbits, however, indicate that cumene elicits maternal toxicity but not developmental toxicity. These studies are summarized below.

A developmental toxicity study of inhaled cumene vapors in rats found maternal toxicity at 500 and 1200 ppm and no developmental toxicity at concentrations up to 1200 ppm. Timed-pregnant Sprague-Dawley rats (25 per group) were exposed to cumene vapor for 6 hours/day on gestational days 6 through 15 at target concentrations of 0, 100, 500, or 1200 ppm. Maternal toxicity was evidenced at 1200 ppm by significant reductions in body weight gain and treatment-related clinical signs of toxicity (perioral wetness and perioral encrustation) following daily exposures as well as during exposures (hypoactivity and blepharospasm), decreased food consumption during the exposure period and increased relative liver weight at necropsy. Reduced food consumption and clinical observations during exposure were observed at 500 ppm as well. In addition, while the increase in relative liver weight was not statistically significant, a 5% increase was part of a dose-related response in that organ. Gestational parameters (e.g., numbers of viable implantations per litter, sex ratio) and fetal body weights (total, males or females) per litter were unaffected by exposure. There were no significant increases in the incidences of individual malformations or of pooled external, visceral or skeletal malformations or of total malformations at any exposure level. There were no treatment-related increases in the incidence of individual variations (external, visceral, or skeletal) or total variations at any dose level. Three skeletal variations (bilobed thoracic centrum #11, poorly ossified parietal bones and bilobed ossification sites in sternebra #5) exhibited significantly reduced incidences which were not exposure related (Neeper-Bradley, 1989a).

In rabbits, inhalation of cumene vapors during organogenesis resulted in consistent maternal toxicity at 2300 ppm and less severe maternal effects at 500 and 1200 ppm. Timed-pregnant New Zealand White rabbits (15 per treatment group) were exposed to cumene vapor for 6 hours/day on gestational days 6 through 18 at target concentrations of 0, 500, 1200, or 2300 ppm. Maternal effects were observed at 500, 1200, and 2300 ppm. Maternal toxicity at 2300 ppm was evidenced by death (2 of 15 doses, 13.3%), significant reductions in weight gain and food consumption during the exposure period, clinical signs

of toxicity both during and subsequent to daily exposures and a significant increase in relative liver weight. At 500 and 1200 ppm, food consumption was consistently reduced during the exposure period. Gestational parameters (e.g., number of corpora lutea; total, nonviable, or viable implantations per litter; sex ratio; pre- or post-implantation loss, and fetal body weights per litter) exhibited no significant changes. There were no significant changes in the incidence of any individual malformations, malformation by category (external, visceral, or skeletal), or of total malformations. There were also no treatment-related changes in the incidence of individual variations, variations by category, or of total variations. An external variation, ecchymosis (a small hemorrhagic spot) of the head was significantly increased at 500 but not 1200 or 2300 ppm and was therefore not considered dose-related (Neeper-Bradley, 1989b).

In a three-generation inhalation reproduction study, male and female Charles River CD rats received whole body exposure to a mixture of C9 aromatic hydrocarbons containing approximately 2.7% cumene, in a dynamic air-flow chamber. Groups of 30 males and 30 females (F0, F1 and F2 generations) were exposed to target concentrations of 0, 100, 500 and 1500 ppm for 6 hours/day, 5 days/week for a 10 to 12 week pre-mating period followed by a 14-day mating period. Mated dams were exposed for 6 hours/day, 7 days/week during days 0 through 20 of gestation, and days 5 through 21 of lactation (dams were separated from their litters during exposure). Effects seen among high-dose animals included increased mortality among all generations of dams, treatment-related changes in the lungs of F0 and F1 animals, and increased salivation, unkempt appearance, body staining, hunched posture, aggressive behavior and hair loss in F1 and F2 animals. Effects seen only in high-dose F1 animals were reduced motor activity and ataxia, and reproductive effects (decreased fertility among males, implantation rate, number of pups delivered, and neonatal survival). Decreased parental body weights were observed in F0, F1 and F2 animals in both mid- and high-dose groups; pups from these groups had a decreased rate of growth. The only effect observed at the 100 ppm level was a decrease in body weight gain for the F2 animals (International and Research and Development Corp., 1989).

Structure/Activity Relationships: Seven compounds structurally similar to cumene were screened for relevant information associating these related chemicals with a mutagenic or carcinogenic effect. A summary of information found in the available literature is presented in Table 1 followed by a more detailed discussion. No information on

carcinogenicity or mutagenicity was found for the following structurally related compounds: *o*-methylcumene [527-84-4], *m*-methylcumene [535-77-3], and *p*-methylcumene [99-87-6]. Information on carcinogenicity was identified for only one of the structurally similar compounds, ethylbenzene. NTP has tested ethylbenzene by inhalation in rats and mice. The Pathology Working Group report is completed but final evaluations are pending. Ethylbenzene was not carcinogenic in rats treated orally. Mutagenicity data were available for three of the seven structurally related compounds. No evidence of mutagenic activity was observed in bacterial tests with ethylbenzene, *n*-propylbenzene, *sec*-butylbenzene, or cymene (mixed isomers). Additional information was available on the mutagenic potential of ethylbenzene. *In vitro*, it induced chromosome damage in human lymphocytes (weakly positive) but not in CHO cells. Ethylbenzene tested positive in the mouse lymphoma assay. In rats and mice exposed via inhalation to ethylbenzene, induction of micronuceli in peripheral blood was not observed.

Table 1. Summary of Information on Cumene and Three Structurally Related Compounds

Chemical [CAS No.]	Carcinogenicity Data	Mutagenicity Data	Other
Cumene [98-82-8]	NDF	negative with or without S9 in *S. typhimurium*, *S. cerevisiae* (Tardiff *et al.*, 1976; Simmon *et al*., 1977; Florin *et al.*, 1980; Flowers, 1982; Lawlor & Wagner, 1987) negative without S9 for increasing the mutagenicity of diesel particle extracts in *S. typhimurium* (Jensen *et al*., 1988) negative with or without S9 in the CHO/HGPRT assay (Gulf Life Sciences Center, 1985a; Yang, 1987) negative with and without S9 for chromosomal aberrations in CHO cells (Putnam, 1987a) negative for induction of micronucleated polychromatic erythrocytes in bone marrow of mice treated *in vivo* (Gulf Life Sciences Center, 1985b) conflicting results on induction of cell transformation in mouse embryo cells (Gulf Life Sciences Center, 1984a; Putman, 1987b) conflicting results on induction of UDS in rat hepatocytes (Gulf Life Sciences Center, 1984b; Curren, 1987)	maternal toxicity but not developmental toxicity in rats and rabbits following inhalation (Neeper-Bradley, 1989a,b)

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Ethylbenzene [100-41-4]	not carcinogenic in rats treated orally (Maltoni *et al.*, 1985) NTP chronic inhalation bioassay completed in rats and mice. Pathology Working Group reports available; final evaluation of strength and significance of findings is pending (NTP, 1995a,b)	negative with and without S9 in *S. typhimurium, E. coli*, and *S. cerevisiae* (NTP, 1992) negative with and without S9 for induction of sister chromatid exchanges and chromosomal aberrations in CHO cells (NTP, 1992) negative for the induction of micronuclei in peripheral blood of rats and mice exposed via inhalation (NTP, 1992) weakly positive with S9 for induction of sister chromatid exchanges in cultured human lymphocytes (NTP, 1992) positive in the mouse lymphoma assay (NTP, 1992)	maternal and developmental toxicity in rats exposed via inhalation (NTP, 1992)
n-Propylbenzene [103-65-1]	NDF	negative with and without S9 in *S. typhimurium* (Florin *et al*., 1980) negative without S9 for increasing the mutagenicity of diesel fuel particle extracts in *S. typhimurium* (Jensen *et al*., 1988)	
sec-Butylbenzene [135-98-4]	NDF	negative without S9 for increasing the mutagenicity of diesel fuel particle extracts in *S. typhimurium* (Jensen *et al*., 1988)	
Cymene, mixed isomers [25155-15-1]	NDF	negative in *S. typhimurium* strains TA98 and TA100: urinary extracts of rats fed the compounds or for the compound itself with S9 (Rockwell & Raw, 1979)	

Ethylbenzene. Ethylbenzene has been tested in the NTP test program by the inhalation route (whole-body exposure target concentrations of 0, 75, 250, or 750 ppm for 6 hours, 5 days/week for 104 weeks) in F344 rats and B6C3F$_1$ mice. The Pathology Working Group found that administraation of ethylbenzene was associated with the following histopathologic lesions:

Rats

1. An increased severity of renal nephropathy in the high dose animals, particularly in the males. This lesion was accompanied by an increased incidence of transitional epithelial hyperplasia. In addition, lesions such as parathyroid gland hyperplasia and uremic related lesions in the lungs (hemorrhage, congestion, edema, inflammation) were increased in the high dose males.

2. The presence and increased incidence of renal tubule proliferative (hyperplasia, adenoma, carcinoma) lesions in the exposed males, particularly in the high dose males. Equivocal increases of some proliferative lesions were present in the mid and high dose females.

3. An increased incidence, not dose-related, of prostate gland inflammation in all dose groups of treated males.

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4. An increased incidence of cystic degeneration in the liver of high dose males.

5. An increased incidence of bone marrow hyperplasia in the low and high dose male animals.

Mice

1. An increased incidence of alveolar/bronchiolar neoplasms in the lungs of exposed male animals, particularly at the 250 and 750 ppm dose levels, and slightly increased in the 750 ppm females. In addition, metaplasia of the alveolar epithelium was also diagnosed primarily in the exposed males.

2. An increased incidence of hepatocellular adenomas/carcinomas in the liver of the 750 ppm females. In addition, lesions such as hepatocellular syncytial alteration, hypertrophy and necrosis were also confirmed in exposed male animals.

3. An increased incidence of thyroid follicular cell hyperplasia in exposed males and females, particularly in the 250 and 750 ppm animals.

4. An increased incidence of pars distalis hyperplasia of the pituitary gland in the 250 and 750 ppm, exposed females.

Evaluation of the strength and significance of the pathology findings must await generation of the final tables and statistical analyses of the data (NTP, 1995a,b).

An oral chronic study found that ethylbenzene was not carcinogenic in male or female CD rats gavaged daily with 500 mg/kg, 4-5 days/week, for 104 weeks (Maltoni *et al*., 1985).

An NTP report summarized NTP-sponsored genotoxicity tests results and test results in the published literature as follows. Ethylbenzene was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA97, and TA98 when tested up to toxic doses (1000 µg/plate) in the presence and absence of S9. It also was reported negative for gene mutation induction with and without S9 in *S. typhimurium* strains TA1537 and TA1538, in *Escherchia coli* WP2 and WP2uvrA, and in *Saccharomyces cerevisiae* JD1. No induction of sister chromatid exchanges or chromosomal aberrations were observed in CHO cells treated with ethylbenzene in the presence (up to 175 µg/ml) or absence (up to 151 µg/ml) of S9, but a weakly positive response was reported for SCE induction in cultured human lymphocytes with S9. An increase in trifluorothymidine-resistant colonies of L5178Y/TK$^{\pm}$ mouse lymphoma cells was observed at the highest nonlethal dose (80 µg/ml) of ethylbenzene tested without S9. NTP-sponsored tests found no induction of micronuclei in peripheral blood erythrocytes of male and female rats and mice exposed to ethylbenzene for 6 hours/day, 5 days/week for 92 to 98 days at concentrations up to 1000 ppm (NTP, 1992).

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An NTP report summarized reproductive toxicity results in the published literature as follows. The offspring of female Wistar rats exposed to ethylbenzene at 1000 ppm, 7 hours/day, 5 days/week, for 3 weeks before mating to normal males, then exposed daily through 19 days of gestation, had a higher incidence of extra ribs. Similar findings were reported in the offspring of CFY rats which were exposed to ethylbenzene at 554 ppm, 24 hours/day, from day 7 to day 15 of gestation. Maternal toxicity was manifested as an increase in liver, kidney, and spleen weights (NTP, 1992).

n-Propylbenzene. In a screening of tobacco smoke constituents for mutagenicity in the Ames assay, *n*-propylbenzene tested negative in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 at concentrations up to 30 µmol/plate both with and without metabolic activation (liver fraction from Aroclor 1254-induced rats in all strains and from methylcholanthrene-induced rats in strains TA98 and TA100); at 3 µmol/plate, toxicity was noted (Florin *et al*., 1980). In addition, *n*-propylbenzene (about 10% by volume) did not increase the mutagenicity of diesel fuel particle extracts in *S. typhimurium* (test strains not specified) when tested without S9 (Jensen *et al*., 1988).

sec-Butylbenzene. sec-Butylbenzene (about 10% by volume) did not increase the mutagenicity of diesel fuel particle extracts in *S. typhimurium* (test strains not specified) when tested without S9 (Jensen *et al*., 1988).

Cymene, mixed isomers. No mutagenic activity toward *S. typhimurium* TA98 or TA100 was observed with urine extracts of rats fed cymene or with cymene in the presence of S9 (Rockwell & Raw, 1979).

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